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Pregnancy-related Acute Kidney Injury in pre-eclampsia: risk factors and renal outcomes

Running headline: Pr-AKI in pre-eclampsia

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ABSTRACT

Pre-eclampsia is a common cause of acute kidney injury in low- and middle-income countries but acute kidney injury incidence in pre-eclampsia, its risk factors and renal outcomes are unknown. A prospective observational multicentre study of women admitted with pre-eclampsia in South Africa was conducted. Creatinine concentrations were extracted from national laboratory databases for women with maximum creatinine of ≥90 µmol/L (≥ 1.02 mg/dL). Renal injury and recovery were defined by Kidney Disease Improving Global Outcomes creatinine criteria. Pre-defined risk factors, maternal and neonatal outcomes were compared between acute kidney injury stages. 15.3% (237/1547) of women admitted with pre-eclampsia met acute kidney injury criteria: 6.9% (n=107) Stage-1, 4.3% (n=67) Stage-2, 4.1% (n=63) Stage-3. There was higher risk of maternal death (n=7; relative risk (RR) 4.3, 95% CI 1.6-11.4) and stillbirth (n=80; RR 2.2, 95% CI 1.8-2.8) in women with acute kidney injury compared to those without. Perinatal mortality was also increased (89/240; 37.1%). Hypertension in a previous pregnancy was the strongest predictor of acute kidney injury Stage-2 or 3 (OR 2.24, 95% CI 1.21-4.17). Renal recovery rate reduced with increasing AKI stage. A third of surviving women (76/230 (33.0%)) had not recovered baseline renal function by discharge. Approximately half (39/76 51.3%) of these women had no further creatinine testing post-discharge. In summary, acute kidney injury was common in women with pre-eclampsia and had high rates of associated maternal and perinatal mortality. Only two-thirds of women had confirmed renal recovery. History of a previous hypertensive pregnancy was an important risk factor.

Keywords: Acute Kidney Injury (AKI), Pregnancy, Pre-Eclampsia, Chronic Renal Insufficiency, Creatinine.

Introduction

The global incidence of pregnancy-related acute kidney injury (AKI) has reduced over recent decades due to improvements in reproductive healthcare.[1–4] Pregnancy-related AKI remains a common cause for requiring dialysis in low- and middle-income countries (LMIC),[3,5,6] and is associated with high rates of maternal and neonatal morbidity and mortality.[5,7] There is limited understanding of underlying risk factors in these settings to enable appropriate triage and targeting of scare resources. In addition currently published studies are predominantly retrospective, are limited by diverse definitions of AKI, and few report incidence according to Kidney Disease Improving Global Outcomes (KDIGO) criteria.[6]

Outside of pregnancy, there is increasing evidence that AKI is a risk factor for chronic kidney disease (CKD),[8,9] and a recent meta-analysis of population studies has reported that CKD is common in low-income countries. Nearly twice as many women of reproductive age in low-income countries have CKD compared to high-income countries (9.0 v 5.9% respectively),[10] but the relationship between pregnancy-related AKI and subsequent CKD in LMIC is unknown.

Worldwide, hypertensive disorders of pregnancy are the most common cause of pregnancy-related AKI.[5,7,11,12] The CRADLE 2 study was a prospective observational cohort of pregnant or post-partum women admitted with pre-eclampsia in three state tertiary maternity units in South Africa (January 2015 to May 2016). National laboratory databases in South Africa hold all routinely collected laboratory data thus facilitating assessment of renal recovery after AKI. The aims of this secondary analysis of CRADLE 2 were to examine the incidence of pregnancy-related AKI according to KDIGO AKI criteria, and to identify risk factors and report renal outcomes of women with pre-eclampsia who developed such AKI.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. The CRADLE 2 trial was a prospective observational cohort study of women admitted with pre-eclampsia at three tertiary hospital sites (Groote Schuur Hospital, Tygerberg Hospital and Kimberley Hospital) in South Africa between January 2015 and May 2016. Any woman with a clinical diagnosis of pre-eclampsia as determined by their healthcare provider during their admission was included. Baseline and admission characteristics recorded were: age, body mass index (BMI), parity, gestation at admission, admission systolic and diastolic blood pressure, highest systolic blood pressure during admission, diastolic blood pressure at highest systolic blood pressure and admission urine dipstick result (1+ to 3+). Pre-specified clinical outcomes were eclampsia, stroke, maximal creatinine ≥90 μmol/l (≥ 1.02 mg/dL) during admission, maternal and perinatal death. Blood pressure was measured using the Microlife CRADLE Vital Signs Alert (VSA), a device validated for use in pregnancy including pre-eclampsia.[13] The study was approved by the ethics committee at each hospital site: Stellenbosch University Ethics Committee (N14/06068), University of Cape Town Ethics Committees (410/2014) and the University of the Free State Ethics Committee (230408-011), individual written consent was obtained at two sites and institutional level consent was granted at the third site. The study was conducted in line with the Declarations of Helsinki. The full findings of the study are published in the Journal of Global Health.[14] The original study was funded by Bill & Melinda Gates Foundation (Grant ID: OPP1086183).

Serial creatinine values including any pre-pregnancy test results up until May 2017 were extracted from national laboratory databases in all women who had a maximum creatinine of ≥90 μmol/L (MaxCr90) during their admission. Haematological and biochemical test results

at time of MaxCr90 were also recorded. At one hospital site (Groote Schuur hospital) where clinical records were available at the time of the study, original clinical notes were reviewed for all women who had a maximum creatinine of ≥90 µmol/L during admission and a random unmatched sample of 100 controls (maximum creatinine <90 µmol/L during admission), with 100 ID numbers selected using the Stata Version 14.2 (StataCorp, College Station, Texas) random uniform() command. Candidate risk factors for obstetric AKI were recorded: maternal age, body mass index (BMI), gravidity, parity, medical comorbidities: anaemia[15] (haemoglobin <9 g/dL), chronic hypertension (documented history or systolic BP >140 or diastolic >90 mmHg before 20 weeks' gestation or taking antihypertensive medication) and HIV status, and documented history of hypertensive disorder in a previous pregnancy. All three hospital sites gave ethical approval for this additional data collection as amendments to the original ethics application. Funding for this sub-study was provided by the British Maternal Fetal Medicine Society and a Royal College of Obstetricians and Gynaecologists travel award.

The Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine criteria were applied to the serial creatinine data to determine AKI stage, renal recovery at discharge and recovery at follow up for all women with a maximum creatinine of ≥90 µmol/L during admission for pre-eclampsia. Baseline creatinine was defined as the single lowest creatinine concentration <90 µmol/L up to two years prior to admission date up until the end of May 2017. Where women had no creatinine value <90 µmol/L recorded, minimum creatinine during admission was used as a proxy for baseline creatinine. Maximal creatinine was defined as the single highest creatinine concentration ≥90 µmol/L during admission. Discharge creatinine was defined as the single lowest creatinine concentration on the last day creatinine was recorded prior to and including day of discharge. Follow up creatinine was defined as the

single lowest creatinine concentration post discharge until the end of May 2017. KDIGO stage was calculated as per KDIGO criteria using ratios of maximum creatinine to baseline creatinine or minimum creatinine with a ratio of greater than 1.5, 2 and 3 denoting Stages-1, 2 and 3 respectively. A rise in serum creatinine concentration of ≥26 µmol/L in 48 hours during admission also denoted stage 1 AKI, and a maximum of >354 µmol/L was classed as Stage-3 AKI. Recovery at discharge or follow up was determined using ratios of creatinine at discharge and follow-up respectively to baseline or minimum creatinine concentration with a ratio of less than 1.5 denoting recovery.

Ordered logistic regression modelling was used to evaluate the association between baseline demographic and clinical characteristics and development and severity of AKI (outcome considered as ordered categories: no AKI, maximum creatinine ≥90 µmol/L but AKI criteria not met, Stage-1 AKI, Stage-2 AKI, Stage-3 AKI). Logistic regression models and AUROC values with 95% confidence intervals (CI) were used to assess correlation between baseline demographic, clinical and admission characteristics and KDIGO score. Non parametric tests (Kruskal-Wallis test) were used to perform simple comparisons between groups. All data manipulation and analysis was performed in Stata Version 14.2 (StataCorp, College Station, Texas).

Results

AKI staging

1547 women with pre-eclampsia were recruited of whom 272 (17.6%) had a maximum creatinine concentration of ≥90 µmol/L (≥ 1.02 mg/dL) during admission. Of these, 15.3% (n=237) had serial changes in serum creatinine concentration consistent with AKI KDIGO

criteria (Figure 1 and Table 1). One woman was excluded from the study as she had only a single recorded creatinine concentration on the national laboratory database. Of the 1547 women recruited, 6.9% (n=107) had Stage-1 AKI, 4.3% (n=67) had Stage-2 AKI and 4.1% (n=63) had Stage-3 AKI. The remaining 35 women had insufficient rise in creatinine concentration to meet criteria for Stage-1 AKI despite a maximum creatinine concentration of ≥90 μmol/L during admission, or had a single creatinine concentration recorded in the national laboratory databases precluding any assessment of dynamic changes. In these 237 women with AKI, creatinine, urea concentrations and white cell count increased across AKI stages and haemoglobin concentration reduced (S1). Of the 32 women with Stage-3 AKI with hospital records available, 4 (12.5%) required dialysis, with median duration of dialysis being 4 days (range 2-5).

Maternal and neonatal outcomes associated with AKI

Baseline demographics, admission characteristics and pregnancy, maternal and neonatal outcomes in the groups are shown in Table 2. Women who developed AKI (Stages 1-3) were more likely to die (risk ratio (RR) 4.3, 95% CI 1.6-11.4, p = 0.003), have had an eclamptic seizure (RR 1.7, 95% CI 1.2-2.4, p = 0.005), a stroke (RR 16.6, 95% CI 1.7-158.8, p = 0.015), have received magnesium sulfate (RR 1.2, 95% CI 1.1-1.2, p <0.001), or be admitted to intensive care (RR 1.9, 95% CI 1.6-2.2, p <0.001) compared to women who did not develop AKI during admission with pre-eclampsia. Overall there were seven maternal deaths in the women who met KDIGO AKI criteria (7/237, 3.0%); with no significant difference between AKI stages (p=0.803). However rates of eclampsia increased with AKI stage (p value for trend = 0.02, Stage-3 v Stage-1 AKI RR 2.3, 95% CI 1.1-4.7, p = 0.02), in parallel with rates of intensive care

unit admission (p value for trend <0.001, Stage-3 v Stage-1 AKI RR 2.1, 95% CI 1.5-2.9, p <0.001, Stage-2 v Stage-1 AKI RR 1.7, 95% CI 1.2-2.4, p = 0.003).

Women who developed AKI were also more likely to experience a stillbirth (RR 2.2, 95% CI 1.8-2.8, p <0.001) compared to women without AKI. This was unchanged by adjustment for maximum systolic blood pressure (BP) during admission, diastolic BP at maximum systolic BP and gestation at admission in models (odds ratio*[1] (OR) 3.32, 95% CI 2.29-4.81, p <0.001). There were no significant differences in rates of neonatal deaths between women with and without AKI (RR 1.5, 95% CI 0.8-3.1, p = 0.229). Stillbirth rates increased significantly with increasing AKI severity (p value for trend = 0.01, Stage-3 v Stage-1 AKI RR 1.7, 95% CI 1.1-2.6, p = 0.008), and adjustment for maximum systolic blood pressure (BP) during admission, diastolic BP at maximum systolic BP and gestation at admission similarly did not alter results (Stage-3 v Stage-1 AKI OR* 2.61, 95% CI 1.29-5.27, p = 0.007). Overall perinatal mortality in babies born to women with AKI including twin pregnancies was 37.1% (89/240).

Risk factors for AKI

Selection for cases and controls at the single hospital site is shown in Figure 2. Original patient files were available for 163/174 (94%) cases with maximum creatinine concentration ≥ 90 µmol/L and 96/100 (96%) randomly selected controls (maximum creatinine < 90 µmol/L). Maternal demographics and co-morbidities by AKI category and stage are shown in Supplementary Table 2. Results of individual ordered logistic regression for each predefined risk factor are shown in Table 3. Following stepwise ordered logistic regression, only history

*[1]Results presented as OR rather than RR as binomial regression models failed to converge.

of prior hypertensive disorder of pregnancy and maternal age were significant predictors of AKI (Table 3). The analysis was repeated using a cutoff point of Stages-2 or more AKI to assess the robustness of this finding, and previous history of hypertensive disorder alone was also predictive of Stage-2 or 3 AKI (Odds Ratio (OR) 2.24, 95% confidence interval 1.21-4.17, Z-score 2.56, p = 0.011).

When post-admission factors (gestation at admission, admission systolic (SBP) and diastolic blood pressure (DBP), admission urine dipstick findings, and maximum SBP and DBP at maximum DBP) were included in the stepwise logistic regression model with predefined risk factors, history of hypertensive disorder of pregnancy and blood pressure variables remained significant predictors (Table 3). Maximum SBP during admission was the best individual predictor of AKI severity with a comparable area under the receiver operator curve (AUROC) to the adjusted prediction model (Table 3).

Renal recovery at discharge and follow up

Renal recovery at discharge or during follow up according to AKI stage is shown in Table 4. Overall 154/230 (67.0%) of surviving women had recovered from AKI at discharge from hospital. Rate of renal recovery at discharge reduced significantly with increasing stage of AKI; 95/105 (90.5%) of women with Stage-1 AKI, whilst only 38/64 (59.3%) women with Stage-2 and 21/61 (34.4%) with Stage-3 AKI had recovered function ($p<0.01$). Of the 76 women who had not recovered renal function at discharge, 39 (51.3%) had no further creatinine concentrations assessed. Of the 37 women with repeat creatinine concentrations post discharge 31 (83.8%) had renal recovery and 6 (16.2%) did not. These six women had all experienced Stage-2 or 3 AKI. For women who recovered renal function after discharge,

creatinine testing confirming recovery was taken at a median of 38 (interquartile range (IQR): 17-208) days following discharge. Overall rate of confirmed renal recovery was higher for Stage-1 AKI (94.3%), compared to Stage-2 (70.3%) and Stage-3 (67.2%) AKI. However, many women did not have creatinine concentration repeated after discharge including 23.4% of women with Stage-2 and 29.5% of women with Stage-3 AKI (Table 4).

Discussion

Principal findings

Fifteen percent of women admitted to hospital with pre-eclampsia in this middle-income country cohort had pregnancy-related AKI assessed by KDIGO criteria, with over half of cases being Stage-2 or 3 in severity. Maternal death, eclampsia, stroke and stillbirth rates were higher in these women than those without. A novel finding of this study was the high proportion of women with pregnancy-related AKI with a history of hypertensive disorder in a previous pregnancy, also more frequent with increasing AKI severity. Approximately two-thirds of women had recovered from AKI at discharge, with lower rates of renal recovery with more severe AKI stages. Overall 2.3% of women had not recovered from AKI on follow up, all of whom had Stage-2 or 3 AKI. However overall rate of renal recovery in those with repeat creatinine concentration testing was high, though over 50% of women with Pr-AKI that had not recovered renal function at discharge had no repeat testing.

Strengths and limitations

The strengths of this study include its large, multicenter, prospective design with comprehensive national laboratory serial creatinine concentration data analysis which allowed KDIGO staging of AKI and analysis of risk factors and outcomes according to AKI stage.

Limitations include all centres being in a single country which means findings may not be generalisable to other low- and middle-income settings. Furthermore, the diagnosis of preeclampsia was a clinical diagnosis determined by healthcare provider rather than application of validated diagnostic criteria. Lack of follow up in over half of women who had not recovered baseline renal function from AKI by discharge from hospital impacted on our ability to determine the overall renal outcomes of AKI. In addition, other clinical events that may have affected development and severity of AKI such as haemorrhage, sepsis, nephrotoxin exposure, HIV viral load and fluid and blood resuscitation, were not captured. Lastly, clinical record review to investigate risk factors for AKI was only possible at one of the three hospital sites where maternity records were available.

We found higher rates of maternal and perinatal death in women with AKI than those without. Small numbers of maternal deaths precluded further analysis of the strongest clinical predictors of this outcome; however our data suggest that AKI may be a useful surrogate marker of maternal disease severity in pre-eclampsia, given the high rates of intensive care admission with increasing AKI severity. The finding of higher rates of perinatal death in women with AKI remained significant after adjustment for BP variables and gestation at admission, demonstrating that AKI is potentially an important independent predictor of poor outcome in the fetus, although further research with more detailed clinical data is required to validate this finding.

Whilst equations used to calculate glomerular filtration rate (GFR) are inaccurate in pregnancy,[16,17] KDIGO AKI criteria have not been formally validated in pregnancy. KDIGO AKI criteria were chosen as this method has gained international consensus.[18] In calculating the

KDIGO score there were a small number of women (n=33), who only had raised creatinine concentrations of ≥90 µmol/L (≥ 1.02 mg/dL) on the National Laboratory databases. It is unknown whether these women had CKD or that KDIGO AKI criteria underestimated AKI severity of these women due to incomplete follow up. Furthermore, preliminary identification of AKI by selection of the predefined outcome of maximum creatinine ≥90 µmol/L may have led to some cases of AKI being missed in women who had an increment in serum creatinine which did not reach this threshold, although the renal implications of this are less clear.

Comparison with other studies

The higher rates of maternal death and stillbirth associated with AKI in our study is in keeping with the findings of a recent systematic review and metanalysis of pregnancy outcomes of Pr-AKI.[6] However, direct comparisons of incidence between studies is challenging due to differing definitions of pregnancy-related AKI.[5,19] Only one study reported outcomes according to KDIGO AKI criteria.[11] Maternal death is reported to occur in up to 20% of cases of pregnancy-related AKI, with dialysis requirements ranging from 0-54.6%[4,9,14] with complete renal recovery in 69.4%[5], 89.4%[7] and 84.6%[9] and dialysis dependence in 1.2%[5] of cases. These diverse outcomes are likely to reflect different aetiologies and definitions of AKI. The high rate of eclampsia within our cohort is in keeping with other published studies of pre-eclampsia from South Africa.[20] The high rate of Caesarean section is not unexpected as the majority of cases were of preterm pre-eclampsia which is often associated with significant placental dysfunction which often precludes vaginal delivery.[21,22]

Established risk factors for AKI in non-pregnant populations include extremes of age, renal insufficiency, hypertension, diabetes, and cardiovascular disease.[23,24] There is a paucity of studies investigating risk factors specifically for AKI within pregnancy. History of a previous pregnancy complicated by hypertension was identified to be associated with AKI in our study. The finding of a previous pregnancy complicated by hypertension as a risk factor for AKI was independent of other risk factors, and was more common with increasing severity of AKI. If post-admission variables were also considered, maximal systolic blood pressure (SBP) alone was the best predictor of AKI and increasing severity of AKI. However of note the models had only modest predictive capacity (AUROC of 0.71 for combined model and 0.66 for maximum SBP alone). Susceptibility to AKI in patients with normal kidney function has recently been proposed to be increased in those with reduced renal reserve i.e. inability to augment glomerular filtration in response to protein loading.[25] It is possible that a renal insult in a previous hypertensive pregnancy lowers functional reserve and contributes to reduced adaptive response in a subsequent pregnancy. Furthermore, pre-eclampsia has been reported to be four-fold more common in women with a previous episode of AKI despite complete resolution of changes in serum creatinine.[26] Thus underlying subclinical renal disease could contribute to both susceptibility to recurrent pre-eclampsia and AKI.

In this study, the majority of women had resolution of AKI where follow-up data were available, with reducing rates of recovery with increasing AKI severity which was also reported in a prospective Indian cohort study. However, incomplete renal recovery at three months postpartum was higher (9.5%) in the Indian cohort in which only 3.5% of women were lost to follow-up[4] compared to incomplete renal recovery (2.6%) in our cohort. This may represent differing AKI severity or an underestimation of persistent renal injury in this study due to inadequate repeat sampling after discharge.

Outside of pregnancy, reported rates of recovery from AKI have varied between 33 and 90%, which is thought to be accounted for by different definitions of both AKI and renal recovery, differences in study populations and differences in timing of assessment,[27,28] but in general appear to be lower than recovery rates for women with Stages-2 and 3 AKI in our study (68.6% confirmed renal recovery). It is possible that pregnancy offers some protection against kidney injury, as suggested by recent work in animal models,[29] and in addition studies of AKI in pregnancy typically involve younger, healthier cohorts than studies of AKI in non-pregnant populations.

Perspectives: Implications for clinicians and future research

Awareness that recurrent pre-eclampsia in a second pregnancy may be associated with higher risk of AKI may be useful in triaging patients, frequency of creatinine concentration testing and determining location of onward referral in LMIC settings. In addition, the association between maximum systolic blood pressure and risk of AKI warrants further investigation including whether controlling blood pressure in hypertensive pregnant women reduces incidence or severity of AKI and other maternal and perinatal morbidities. Further research is required to determine the short- and long-term outcomes of pregnancy-related AKI, and whether this differs according to underlying aetiology. Whilst currently the outcomes of this condition are not fully understood, we would encourage clinicians to follow up women who have experienced AKI who have not recovered renal function at discharge. The relationship between hypertensive disorders of pregnancy and renal reserve should be explored.

Conclusions

Our study has identified that in a middle-income setting, pregnancy-related AKI complicates approximately 15% of admissions with pre-eclampsia, and over half of these cases are severe (Stage 2 or 3 AKI) with high rates of associated maternal (3.0%), and perinatal (37.1%) mortality. History of a previous hypertensive disorder of pregnancy was the most significant risk factor for development of AKI and worsening AKI severity. Approximately two thirds of women had recovered from AKI at discharge, but further studies are required to determine the short term and long term renal outcomes of pregnancy-related AKI.

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Disclosures of interest

The authors report no conflicts of interest.

Contributions to authorship

Conception: KB, FCR, LCC, HLN, AHS. Design: KB, FCR, LCC, HLN, AHS. Data acquisition: FCR, AD, DH. Analysis and interpretation: FCR, PS, KB. Input into drafting the article: FCR, KB. Revision and final approval of the article: FCR, KB, LCC, PS, HLN, AHS, AD, DH.

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Novelty and Significance

1) **What is new?**

The novel finding of this study was the high proportion of women admitted with pre-eclampsia who developed AKI that had a history of hypertensive disorder in a previous pregnancy, which was more frequent with increasing AKI severity.

2) **What is relevant?**

This study demonstrates the significant burden of morbidity of hypertensive disorders of pregnancy in middle income settings; fifteen percent of women admitted to hospital with pre-eclampsia had pregnancy-related AKI assessed by KDIGO criteria, with over half of cases being Stage-2 or 3 in severity. Maternal death, eclampsia, stroke and stillbirth rates were all higher in these women than those without.

3) **Summary**

This study has identified that in a middle-income setting, pregnancy-related AKI complicates approximately 15% of admissions with pre-eclampsia, and over half of these cases are severe (Stage 2 or 3 AKI) with high rates of maternal (3.0%), and perinatal (37.1%) mortality. History of a previous hypertensive disorder of pregnancy was the most significant risk factor for development of AKI and worsening AKI severity. Approximately two thirds of women had recovered from AKI at discharge, but further studies are required to determine the short term and long term renal outcomes of pregnancy-related AKI.

Tables

Table 1. AKI staging as per definitions in Box 1. Results displayed as n (percentage of total cohort).

KDIGO AKI Stage	Baseline creatinine available	No baseline (minimum creatinine used)	Total (n(%))
1	92 (5.9)	15 (1.0)	107 (6.9)
2	60 (3.9)	7 (0.5)	67 (4.3)
3	55 (3.6)	8 (0.5)	63 (4.1)
No AKI			
MaxCr <90 µmol/L	-	-	1275 (82.4)
MaxCr ≥ 90 µmol/L, did not meet AKI criteria	31 (2.0)	3 (0.2)	34 (2.2)
Unable to score (single creatinine value)	-	-	1 (0.1)
TOTAL	**238 (15.4)**	**33 (2.1)**	**1547 (100)**

Table 2. Maternal demographics, admission characteristics and delivery, maternal and neonatal outcomes by AKI category and AKI stage as defined by KDIGO in women with pre-eclampsia. Results are presented as mean [standard deviation] or n (percentage).

Demographic, admission, delivery and outcome variables	**No AKI**		**AKI stage**		
	MaxCr <90 (n=1275)	MaxCr ≥90, AKI criteria not met (n=35)	Stage 1 (n=107)	Stage 2 (n=67)	Stage 3 (n=63)
Baseline reference creatinine	-	-	70 [23]	61 [41]	59 [35]
Time reference creatinine taken: Pre-pregnancy Antenatal prior to admission During admission Postpartum after discharge	-	-	2 (1.9) 18 (16.8) 86 (80.4) 1 (0.9)	3 (4.5) 19 (28.4) 45 (67.2) 0 (0.0)	1 (1.6) 10 (15.9) 52 (82.5) 0 (0.0)
Maternal demographics (n = 1547 women)					
Age at admission, year	27.5 [6.2]	26.6 [6.9]	28.4 [6.2]	28.8 [6.1]	27.4 [5.7]
Body mass index, kg/m²*	30.5 [7.9]	26.6 [6.2]	29.4 [7.2]	31.4 [6.8]	28.9 [6.4]
Primiparous*	480 (37.6)	17 (48.6)	33 (30.8)	18 (26.9)	16 (25.4)
Admission characteristics (n = 1547 women)					
Gestation at admission, weeks*	33.0 [4.9]	31.9 [4.4]	31.6 [5.0]	32.6 [4.3]	31.6 [5.3]
Admission systolic BP, mmHg*	149 [19]	147 [18]	152 [24]	157 [27]	160 [31]
Admission diastolic BP, mmHg*	96 [14]	96 [15]	99 [18]	104 [19]	105 [23]
Admission urine dipstick* 1+ 2+ 3+ Trace/negative Missing	 166 (13.0) 495 (38.8) 457 (35.8) 152 (11.9) 5 (0.4)	 3 (8.6) 10 (28.6) 17 (48.6) 3 (8.6) 2 (5.7)	 11 (10.3) 41 (38.3) 52 (48.6) 3 (2.8) 0 (0.0)	 8 (11.9) 18 (26.9) 39 (58.2) 2 (3.0) 0 (0.0)	 8 (12.7) 14 (22.2) 36 (57.1) 5 (7.9) 0 (0.0)
Delivery and maternal outcomes (n = 1547 women)					
Maximum systolic BP, mmHg*	170 [15]	172 [17]	178 [18]	181 [22]	187 [25]
Maximum diastolic BP, mmHg*	103 [14]	105 [18]	109 [16]	111 [18]	111 [21]
Mode of delivery Caesarean section Vaginal delivery Missing	 899 (70.5) 374 (29.3) 2 (0.2)	 26 (74.3) 9 (25.7) 0 (0.0)	 72 (67.3) 35 (32.7) 0 (0.0)	 47 (70.1) 20 (29.9) 0 (0.0)	 37 (58.7) 26 (41.3) 0 (0.0)
Eclampsia*	110 (8.6)	3 (8.6)	11 (10.3)	8 (11.9)	15 (23.8)
Stroke*	1 (0.1)	0 (0.0)	0 (0.0)	3 (4.5)	0 (0.0)
Maternal death*	8 (0.6)	1 (2.9)	2 (1.9)	3 (4.5)	2 (3.2)

ICU admission*	327 (25.6)	11 (32.4)	35 (32.7)	37 (55.2)	43 (68.3)
Use of magnesium sulfate*	1082 (84.8)	31 (91.2)	105 (98.1)	64 (95.5)	63 (100)
Neonatal outcomes (n = 1589 babies)					
No. of babies	1310	39	108	69	63
Perinatal mortality					
Stillbirth*	194 (14.8)	7 (18.0)	30 (27.8)	20 (29.0)	30 (47.6)
Neonatal death	41 (3.7)	1 (3.1)	4 (5.1)	3 (6.1)	2 (6.1)

MaxCr: maximum creatinine concentration in µmol/L. SBP: systolic blood pressure. DBP:

diastolic blood pressure. ICU: Intensive Care Unit. * = significant differences ($p < 0.05$)

between AKI and non AKI groups

Table 3. Results of individual and stepwise ordered logistic regression and area under the receiver-operator curve (AUROC) for pre-defined clinical predictors, with and without admission and post-admission variables included in models, for development of AKI and increasing AKI severity.

Predictors: pre-defined	**Odds Ratio**	**95% confidence interval**	**Z – score**	**P - value**
Individual ordered logistic regression				
Anaemia (Hb <9g/dL)	1.22	0.47-3.16	0.42	0.678
HIV	1.31	0.65-2.64	0.74	0.457
Primiparous	0.72	0.45-1.13	-1.43	0.152
Parity (increasing)	1.24	1.01-1.51	2.09	**0.037**
Gravidity (increasing)	1.21	1.03-1.42	2.28	**0.023**
Chronic hypertension	1.99	1.16-3.40	2.51	**0.012**
History hypertensive disorder of pregnancy	2.10	1.25-3.52	2.79	**0.005**
BMI category	0.92	0.76-1.11	-0.87	0.383
Age category	1.04	1.01-1.08	2.60	**0.009**
Stepwise ordered logistic regression				
History of hypertensive disorder of pregnancy	1.87	1.10-3.18	2.30	**0.021**
Age category	1.03	1.00-1.07	2.09	**0.037**
Predictors: Pre-defined, admission and post admission	**Odds Ratio**	**95% confidence interval**	**Z – score**	**P - value**
Stepwise ordered logistic regression				
Admission SBP	0.99	0.98-0.99	-2.14	**0.032**
DBP at maximum SBP	1.02	1.00-1.04	2.48	**0.013**

History of hypertensive disorder of pregnancy	1.95	1.15-3.32	2.48	**0.013**
Maximum SBP	1.03	1.01-1.04	3.26	**0.001**
Area under the receiver-operator curve	**AUROC**	**95% confidence interval**		
Maximum SBP alone	0.66	0.59-0.73		
Prediction model (containing all variables above)	0.71	0.64-0.77		

HIV: Human Immunodeficiency Virus; BMI: Body mass index; DBP: diastolic blood pressure.

SBP: systolic blood pressure.

Table 4. Maternal deaths and renal recovery at discharge, follow up and overall in surviving women by AKI stage. *The p-value for trend in rate of recovery at discharge by AKI stage is <0.01.

Maternal and renal outcomes	**KDIGO Stage**			
Maternal deaths	**Stage 1 (n=107)**	**Stage 2 (n=67)**	**Stage 3 (n=63)**	**Stages 1-3 (n=237)**
Maternal deaths prior to discharge	2 (1.9)	3 (4.5)	2 (3.2)	7 (3.0)
Renal recovery	**Stage 1 (n=105)**	**Stage 2 (n=64)**	**Stage 3 (n=61)**	**Stages 1-3 (n=230)**
Recovered at discharge (n,%)	95 (90.5)*	38 (59.3)*	21 (34.4)*	154 (67.0)
Additional recovery at follow up (n,%)	4 (3.8)	7 (10.9)	20 (32.8)	31 (13.5)
Not recovered at follow up (n,%)	0 (0.0)	4 (6.3)	2 (3.3)	6 (2.6)
Not recovered at discharge with no follow up (n,%)	6 (5.7)	15 (23.4)	18 (29.5)	39 (17.0)
Confirmed renal recovery (n,%)	99 (94.3)	45 (70.3)	41 (67.2)	185 (80.4)